High order time-stepping methods for cardiac electrophysiology models

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Problematic of the time numerical integration in cardiac electrophysiology

Ionic models :
- Stiff differential equations
- Large system
- Highly nonlinear

Numerical contraints :
- Stability + accuracy require fine grid

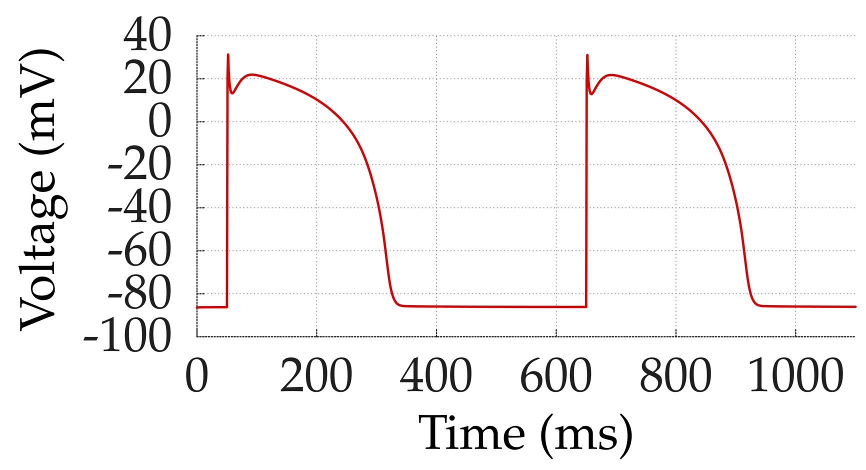
Numerical consequences :
- High CPU cost
- Lack of precision
- Conditioning problems

Questions:
- How can we cope this situation?
- Can high order solver (s) be a solution?

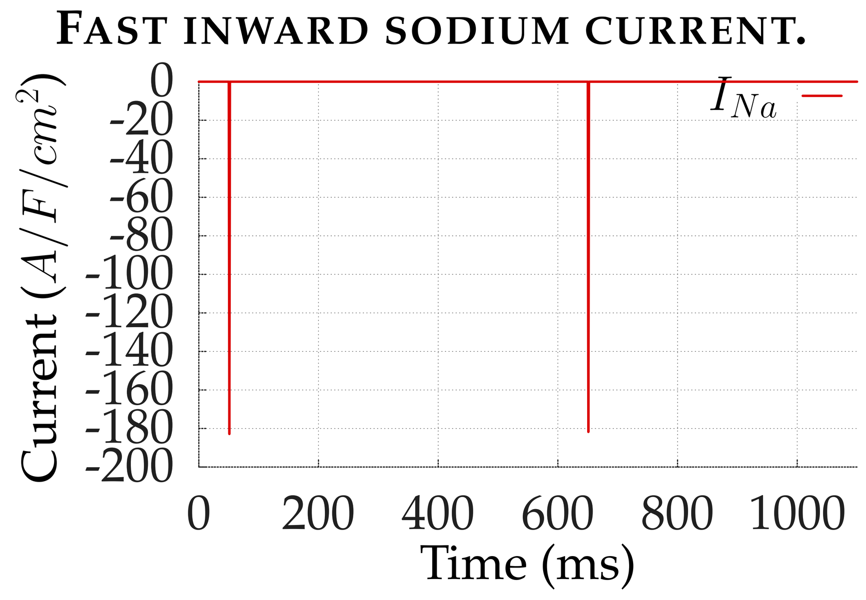
The problem

Example ionic model (TNNP)

Transmembrane potential V.



Fast inward sodium current.



Behavior of the physiological parameters :
- Different time and space scales.
- Fast and slow variables.
- Stiff wave fronts.

Numerical consequences :
- Numerical instabilities.
- High computational cost.
- Significant loss of accuracy

State of the art

Stabilization principle and some stabilized solvers

Equation on gating variables :

$$\frac{dW}{dt} = \frac{W_\infty(V) - W}{\tau(V)}.$$

Forward Backward scheme :

$$\frac{W^{n+1} - W^n}{\Delta t} = \frac{W_\infty(V^n) - W^{n+1}}{\tau(V^n)}.$$

This scheme allows large Δt, linear part $= \frac{-1}{\tau(V)}$.

Linear part known at time $t_n \Rightarrow$ Stabilization.

Order one solvers :
- Forward backward Euler
- RL1: Rush Larsen (1978).

Order two solver :
- RL2: Perego and Veneziani (2009).

High order methods :
- Exponential integrator of Adams type: Norsett (1969).
- Exponential Runge kutta and exponential multi-step (the last ten years).

An innovative method

High-order Rush Larsen methods

Consider the problem,

$$y' = a(t,y)y + b(t,y), \; y(0) = y_0,$$

transformed in each time discretization interval $(t_n, t_{n+1}]$ into,

$$y' = \alpha_n y + c_n(t,y),$$

with $c_n(t,y) = (a(t,y) - \alpha_n)y + b(t,y)$ and α_n a stabilizer. For $t \in (t_n, t_{n+1}]$, the exact solution of this problem satisfies the *variation of constant* formula

$$y(t) = e^{A(t)}(y_n + \textstyle\int_{t_n}^{t} e^{-A(\tau)}c_n(\tau,y)d\tau),$$

with $A(t) = \alpha_n(t - t_n)$. If we set $t = t_{n+1}$ and approximate c_n by a constant β_n , we obtain the following definition of RL_k

$$y_{n+1} = y_n + h\varphi_1(\alpha_n h)(\alpha_n y_n + \beta_n).$$

$\varphi_1(z) = \frac{e^z - 1}{z}$, α_n and β_n are set so that the convergence order k is ensured.

Rush Larsen order 3

$$\alpha_n = \frac{1}{12}(23a_n - 16a_{n-1} + 5a_{n-2}),$$
$$\beta_n = \frac{1}{12}(23b_n - 16b_{n-1} + 5b_{n-2}) + \frac{h}{12}(a_n b_{n-1} - a_{n-1}b_n).$$

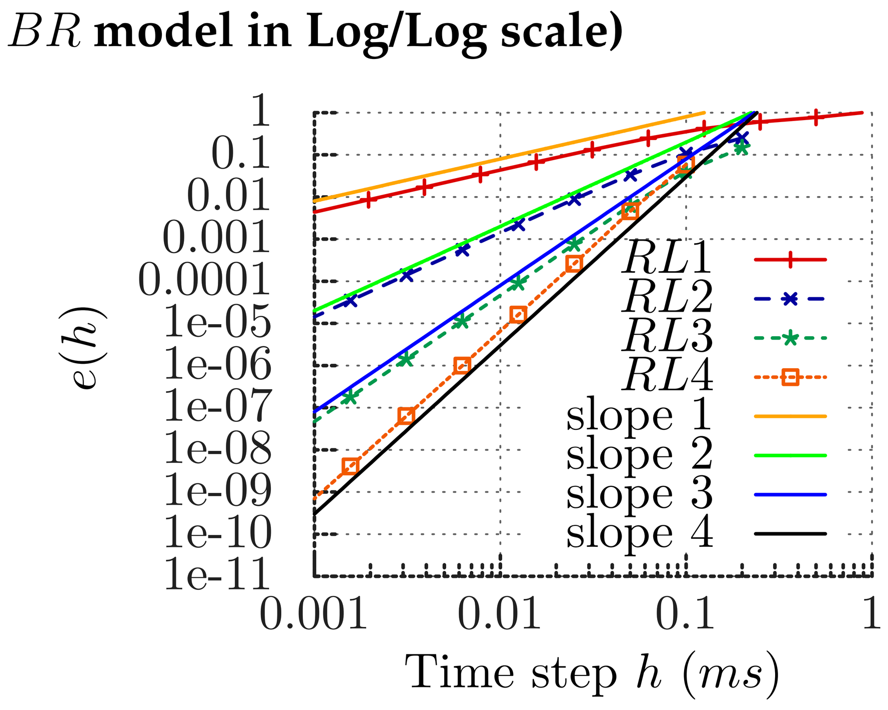
Scheme properties

Advantages and convergence

- Explicit k-multi-step method: $y_n, y_{n-1}, \ldots, y_{n-k+1} \to y_{n+1}$.
- Stability: The same critical time-step as the implicit schemes.
- Easy to implement.
- Cost: one evaluation of the model at every time step (minimal).

Theorem. The RL_k scheme is stable under perturbation and converges with an error of order k, under the assumptions that $a(t,y)$ and $b(t,y)$ in the previous problem are C^k functions and its solution $y(t)$ is defined in $[0,T)$.

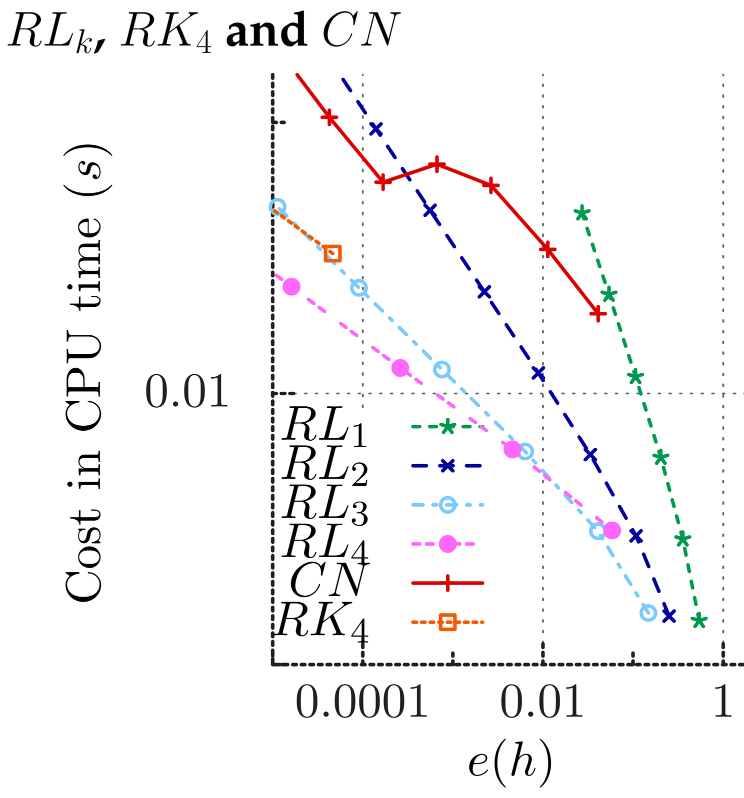
Numerical illustration (Relative error for the BR model in Log/Log scale)



CPU cost

Comparisons

CPU time plotted in Log/Log scale against the error for RL_k, RK_4 and CN



Discussion and conclusion

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Discussion:
- Ionic models are very stiff $\Rightarrow$ classical explicit numerical solver must use small time-steps for stability $\Rightarrow$ **Large CPU time.**
- **High order RL_k remain stable for large time-steps. Their critical time-steps don't depend on the stiffness but on the stabilizer's choice.**

Conclusion:
- We found that high order RL_k is a good alternative to improve the accuracy with neglibible additional cost w/r to RL1 scheme.
- High order RL_k allow the use of large time steps unlike classical explicit schemes. They are suitable for solving stiff ODE.
- High order schemes in cardiac electrophysiology may allow more reliable simulations of long lasting events.

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